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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/945,459	12/09/1997	FUSAO MAKISHIMA	146.1275	2741

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/945,459	MAKISHIMA ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-66* is/are rejected.

7)☒ Claim(s) *54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/17/2005 has been entered.

Claims 49–66 are pending and being examined.

Response to Arguments

Applicants' argue that the activity profiles of methionine aminopeptidase and aminopeptidase-P, as evidenced by Klein's (J Biol Chem. 2003 Nov 28;278(48):47862-7) Fig. 5 and Yaron's (Methods in Enzymology, 1970, 19:521-534) Fig. 1(a), and the pH dependence of MP52's solubility, as evidenced by Kohnert's (WO 03/043673) Figures 1 and 2, are evidence that one of ordinary skill in the art could not obtain an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein proteins according to SEQ ID NO: 1 with either a) an Ala or b) a Met-Ala at the N-terminus are not present in said isolated protein, by the procedures relied upon in the rejection of claim 49 under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (U. S. Patent No. 5,658,882), Ben-Bassat (J Bacteriol. 1987 Feb;169(2):751-7), and Hirel (Proc Natl Acad Sci U S A. 1989 Nov;86(21):8247-51)} in view of Georgiou (AIChE J (1988) 34:1233–1248)] and further in view of Thompson (U. S. Patent No. 5,143,829) and Tonouchi (J Biochem (Tokyo). 1988 Jul;104(1):30-4). These arguments are persuasive.

Maintained Formal Matters, Objections, and/or Rejections:

Double Patenting

Claims 49-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 17 of copending Application No. 10/365,231. Applicants' intent to file a terminal disclaimer is acknowledged.

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 112

Claims 51–66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising the protein of claim 50, in combination with a pharmaceutical carrier, does not reasonably provide enablement for a pharmaceutical composition comprising the protein of claim 50 in an amount effective to treat cartilage and/or bone disease, in combination with a pharmaceutical carrier. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are directed to or encompass a pharmaceutical composition comprising an amount of MP-52/GDF-5/CDMP-1 effective to treat any and/or all cartilage and/or bone diseases, osteoporosis, osteoarthritis, arthrosteitis, any and/or all bone or cartilage defects or lesions, any and/or all articular cartilage or meniscus lesions, any and/or all radicular or alveolar defects, any and/or all congenital cartilage and/or bone diseases, chondrodysplasia, chondrohypoplasia, achondrogenesis, palatoschisis and osteodysplasia. The claims encompass and/or imply preventing, alleviating, treating or curing such diseases and/or conditions in a mammal. Enablement of the claims is evaluated based on such uses.

The specification indicates that MP-52 was confirmed to have cartilage and bone morphogenetic activity (page 3, lines 10-12). The specification further speculates that MP-52 is useful for the treatment of the conditions listed above because of its cartilage and bone morphogenetic activity (paragraph bridging pages 3-4). The examiner is aware of the specification's determination of the biological activities (pages 15-22). However, there are no working examples of the treatment of any and/or all of the conditions listed above. The examiner is also aware that the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art.

GDF-5/CDMP-1 initiates and promotes chondrogenesis and to a limited extent osteogenesis in vitro and in vivo. This makes this polypeptide a potential therapeutic agent in the regeneration of skeletal tissues. However, the use of GDF-5/CDMP-1 as a therapeutic agent is still speculative. Owing to its relationship with other BMPs and its chondrogenic/osteogenic activities, one can envision GDF-5/CDMP-1 as a useful therapeutic agent in protocols designed to enhance cartilage and maybe endochondral bone formation. The use of "devices" enriched with recombinant protein to promote skeletal repair is a logical extension of its biological activities. GDF-5/CDMP-1 might have some advantage in the repair of the cartilaginous skeleton, including the joint surface, because of its apparent preferential promotion of chondrogenesis and maintenance of the cartilage phenotype *in vitro*. Appropriate *in vivo* experiments will allow evaluation of this potential. See Luyten (Int J Biochem Cell Biol. 1997 Nov;29(11):1241-4), Abstract and page 1244, paragraph bridging left and right columns.

Vertebrate limb development is a complex process that involves several regulatory pathways, involving growth factors, morphogens, transcription factors, and homeobox genes. Cartilage-derived morphogenetic protein 1 (CDMP1) is only one of several molecules that have been identified as regulators of limb skeletogenesis and appendicular bone development. See Faiyaz-Ul-Haque (Am J Med Genet. 2002 Jul 22;111(1):31-7), page 31, right column, full paragraph 1.

The development of the appendicular skeleton is influenced by factors distinct from those of the craniofacial and axial skeleton. hCDMP-1 is involved in determining the size and shape of the digits and the observation of joint dysplasia alludes to an additional function in peripheral joint morphogenesis. See Thomas (Nat Genet. 1997 Sep;17(1):58-64), page 317, left column, last full paragraph.

The countervailing evidence that the use of GDF-5/CDMP-1 as a therapeutic agent is still speculative, that vertebrate limb development is a complex process and that the development of the appendicular skeleton is influenced by factors distinct from those of the craniofacial and axial skeleton supports the conclusion that a skilled artisan would not have believed, at time the application was filed, that MP-52 would be effective in treating the list of conditions provided by the intended uses of the claimed compositions. The allegation that, because of its cartilage and bone morphogenetic activity, MP-52 is useful for treatment of the intended uses amounts to showing that it is not implausible that MP-52 will work for its intended purpose. However, showing that it is not implausible that MP-52 will work for its intended purpose is not sufficient to meet the enablement requirement because the countervailing evidence shows that a person of ordinary skill in art would not accept such allegations as obviously correct. Therefore,

Applicants have not established enablement of the intended uses of the claimed pharmaceutical compositions. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to inventions consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the inventor would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis.

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor and the complexity in the art it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

Claim Objections

Claim 54 is objected to because of the following informalities: "lesions" (line 2) is misspelled. Appropriate correction is required.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
FEBRUARY 3, 2006